Drug Interactions and Anti-infective Therapies

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Drug interactions are an important and often underappreciated cause of adverse clinical outcomes. This review considers the mechanisms for several clinically important drug interactions that involve the major classes of anti-infective agents. This approach is intended to complement the use of text-based references and computer databases so that physicians and pharmacists can avoid prescribing and dispensing drugs that have adverse interactions. Am J Med. 1999;106:227–237. ©1999 by Excerpta Medica, Inc.

Current guidelines of the Joint Commission on Accreditation of Healthcare Organizations include criteria for active surveillance and preventive intervention for drug-drug interactions. Although there are many examples of desirable interactions among drugs, including cancer chemotherapy, antihypertensive regimens, and antibiotic combinations (1), this review will focus on those pharmacokinetic interactions involving anti-infective drugs that have important adverse clinical consequences. Each member of a drug pair will be referred to either as an object drug or as a precipitant drug: the effect of the object drug is modified by the precipitant drug (or nutrient or other substance) (2). Occasionally, a pair of drugs will interact in both directions.

Hansten (3) emphasizes several general characteristics of drug interactions. First, there can be wide interindividual and day-to-day intraindividual variations in the interactions. Second, drug interactions may be subtle, are often not easily measurable, and are frequently not detected. Third, a potential interaction may not contraindicate the use of a pair of drugs as long as there is heightened physician awareness, monitoring, and possibly adjustment of dosing. Fourth, most drug interactions are dose-related and may be delayed for days or weeks. Finally, although there may be similarities within a drug class, all members of that class do not necessarily interact in the same way. In addition, undescribed interactions may occur, especially with newly available drugs, over-the-counter drugs (4), or undisclosed “alternative therapies” (5,6).

GENERAL MECHANISMS OF DRUG INTERACTIONS

Drug interactions are classified as pharmacokinetic, pharmacodynamic, or occasionally both (2,3,7–12). Pharmacokinetic interactions occur when the precipitant drug modifies the object drug’s absorption, distribution, metabolism, or excretion. By contrast, in pharmacodynamic interactions, the kinetics of the object drug are not altered, but the precipitant drug changes the effects of the object drug, such as when an aminoglycoside antibiotic potentiates the neuromuscular blocking effects of succinylcholine or a nondepolarizing muscle relaxant (2,13). The most important object drugs involved in either pharmacokinetic or pharmacodynamic interactions are those with a low therapeutic index; thus minor changes in drug levels or effects matter more.

Pharmacokinetically measurable drug interactions do not necessarily result in adverse clinical consequences. This review will emphasize interacting pairs of drugs that have a rating of 1 (major severity) or 2 (moderate severity) with established, probable, or suspected documentation of significance according to the current edition of Drug Interaction Facts (2), or that have a rating of 1 (avoid) or 2 (usually avoid) in the current edition of Hansten and Horn’s Drug Interactions Analysis and Management (13). In addition, some drug pairs whose interactions are rated 3 (minimize risk by heightened monitoring or choosing alternative drugs) by Hansten and Horn will also be mentioned (13). The January 1998 edition of The Medical Letter Drug Interaction Program (14) was used as a supplemental resource.

Altered Bioavailability of Orally Administered Drugs

Anticholinergics, opiates, and food slow gastric emptying, which may delay the time to peak level and reduce the peak concentration of many drugs, while not usually reducing the area under the plasma drug concentration curve. Conversely, prokinetic drugs such as erythromycin, cisapride, or metoclopramide accelerate gastric emptying and delivery of drugs to the small intestine, often resulting in a shorter time to peak level and a greater peak
concentration, again without necessarily changing the net absorption.

In about 10% of people who take digoxin, as much as 40% of the drug is converted by upper intestinal bacteria (Eubacterium lentum and perhaps others) to inactive digoxin reduction products. The growth of those bacteria can be inhibited by orally administered antibiotics, resulting in greater bioavailability of pharmacologically active digoxin (15). Co-administration of oral neomycin, erythromycin, or tetracyclines has resulted in digitalis toxicity, and diminished digoxin metabolism in the gut may persist for months following cessation of the antibiotic (2).

Gastric pH is important in the solubility or chemical stability of some oral antimicrobials, notably certain azole antifungals and beta lactam antibiotics. The bioavailability of these drugs may be altered by antacid therapy. Cationic (especially magnesium or aluminum but also, to a lesser degree, calcium) antacids, sucralfate (sucrose aluminum sulfonate), or perhaps kaolin-pectin also, to a lesser degree, calcium) antacids, sucralfate (sucrose aluminum sulfonate), or perhaps kaolin-pectin form insoluble chelates with certain antibiotics including tetracyclines, fluoroquinolones, and perhaps lincosamides (16), reducing the absorption of the antibiotic (2,17).

Displacement from Plasma Protein Binding Sites Most drugs are reversibly bound to some degree to plasma proteins, principally albumin or α1-acid glycoproteins. It had been thought that displacement from protein binding of one drug by another was a frequent cause of adverse drug interactions. While this may be true in neonates, in adults redistribution and excretion of the object drug quickly occurs. The effects of a transient rise in unbound concentration of the object drug are seldom clinically important (18,19).

Enzymatic Biotransformation: The Cytochrome P450 System

Biotransformation of drugs refers to the oxidation or other enzymatic modification of a compound to one that is more polar and thus more easily excreted either by the liver or kidney. A second phase that may occur is hepatic conjugation of the oxidized drug by either glucuronidation, acetylation, or sulfation. The oxidative phase is a function of hepatic or intestinal cytochrome P450 (mixed-function oxidase) enzymes, which are versatile in their substrate specificity. The P450 system is a “superfamily” of genes encoding isoenzymes that can be grouped by their amino acid sequence homology, substrate specificity, catalytic activity, and inactivation by specific antibodies in vitro. The ability to group these enzymes at a molecular level has allowed a classification schema that is now universally accepted, supplanting earlier names for individual enzymes (20,21). At least 12 families have been described in humans, of which those numbered CYP1, 2, and 3 constitute 70% of the P450 enzyme in human liver and intestinal mucosa and account for nearly all of the known, clinically important, oxidative biotransformations of drugs (10,12).

Many P450 enzymes can be inhibited by precipitant drugs that may or may not also be substrates for the enzymes. This inhibition may result in decreased metabolism of other drugs, causing their accumulation and perhaps toxicity. Furthermore, some P450 subfamilies, on extended exposure to certain drugs or other substances, may be induced to a greater rate of enzyme synthesis, resulting in accelerated metabolism and diminished pharmacologic effects of object drugs (Table 1). The inhibition or induction of certain P450 isoforms by drugs is generally regarded as the most important mechanism of drug interaction, and many of these involve anti-infective agents.

The P450 families or subfamilies that are most involved in adverse drug interactions are CYP1A2, the CYP2C subfamily, CYP2D6, and the CYP3A subfamily (principally CYP3A4). There is as much as a 10-fold interindividual variation in P450 subfamily content. This variation, and the presence of alternative metabolic or elimination pathways for many drugs, may account for the perceived infrequency of serious drug interactions and their unpredictability in an individual patient.

Altered Renal Excretion

Decreased glomerular filtration results in accumulation of drugs that do not have an alternative route of excretion; to the extent that drug interactions are often dose or concentration related, renal failure can predispose a patient to adverse drug interactions. In addition, interference with renal excretion of drugs can cause drug inter-

<table>
<thead>
<tr>
<th>Inhibitors</th>
<th>Inducers</th>
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<tbody>
<tr>
<td>Amiodarone</td>
<td>Barbiturates</td>
</tr>
<tr>
<td>Azole antifungals</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Dexamethasone</td>
</tr>
<tr>
<td>Ciprofloxacin/enoxacin</td>
<td>Ethanol (chronic)</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Grapefruit juice</td>
<td>Rifampin/rifabutin</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Troglitazone</td>
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<tr>
<td>Macrolides</td>
<td></td>
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<tr>
<td>Metronidazole</td>
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<tr>
<td>Propranolol</td>
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<tr>
<td>Sulfonamides</td>
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<td>Trimethoprim</td>
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<tr>
<td>Protease inhibitors</td>
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<tr>
<td>Quinidine</td>
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<tr>
<td>SSRIs</td>
<td></td>
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<tr>
<td>Verapamil</td>
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<tr>
<td>Zafirlukast</td>
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</table>

SSRIs = selective serotonin reuptake inhibitors.
action by competition for renal tubular reabsorption. For example, methotrexate is eliminated by glomerular filtration and tubular secretion. Among antimicrobial drugs, competitors for methotrexate excretion include sulfonamides, trimethoprim, and rarely penicillins. All have been associated with methotrexate toxicity that may be dose-related, as patients on low-dose methotrexate (for rheumatic diseases) are less likely to encounter these interactions than those on high doses for antineoplastic therapy (2,13,14).

Probencid inhibits tubular secretion of organic acids and inhibits hepatic glucuronidation of certain drugs, including zidovudine. It is used intentionally to inhibit renal clearance of cidofovir and penicillins.

Potassium supplements augment the well-known potassium-retaining effects of spironolactone, amiloride, triamterene, and angiotensin-converting enzyme inhibitors. Also, trimethoprim can cause hyperkalemia as a result of a distal renal tubular reabsorptive effect much like amiloride, so potassium supplementation should be undertaken cautiously in patients chronically treated with trimethoprim.

COMMON DRUG INTERACTIONS WITH ANTI-INFECTIVE AGENTS

Fluoroquinolones

Fluoroquinolones as object drugs. The bioavailability of orally administered fluoroquinolones, especially ciprofloxacin, is impaired by coadministration with divalent or trivalent cations because of the formation of nonabsorbable chelates in the upper intestine. Aluminum- or magnesium-containing antacids can decrease the bioavailability of fluoroquinolones by as much as 90%. Sucralfate (sucrose aluminum sulfate), calcium (antacids, calcium supplements, milk, yogurt), iron, zinc, and bismuth may result in a more modest but still significant decrease in absorption of fluoroquinolones, and treatment failures have occurred (22). These interactions can be minimized or avoided by staggered dosing of the fluoroquinolone and the interacting agents.

Fluoroquinolones as precipitant drugs. The most important interaction of fluoroquinolones as precipitant drugs is the ability of enoxacin, ciprofloxacin, and to a lesser extent, norfloxacin to inhibit the metabolism of theophylline by CYP1A2, resulting in theophylline accumulation and toxicity. The newer fluoroquinolones (ofloxacin, levofloxacin, and sparflloxacin) do not inhibit CYP1A2 and do not interact with theophylline to any substantial degree (23). Co-administration of cimetidine, which also is a P450 inhibitor, may aggravate the fluoroquinolone-theophylline interaction. Seizures developed in a patient who had been treated with a combination of ciprofloxacin and theophylline but who had a therapeutic theophylline level. This suggests that there may also be a pharmacodynamic interaction (24) perhaps caused by additive antagonism of the neurotransmitter action of γ-aminobutyric acid (25).

There are several other relatively minor interactions involving fluoroquinolones as precipitant drugs. The effect of fluoroquinolones on anticoagulation with warfarin is modest, rarely reported, and subject to large inter-individual variation (2). Enoxacin as well as ciprofloxacin, but not other fluoroquinolones, inhibit CYP1A2 metabolism of caffeine, prolonging its half-life fourfold to fivefold and increasing its maximum concentration. Case reports or small studies suggest that ciprofloxacin may change the pharmacokinetics of metoprolol, propranolol, mexiletine, diazepam, and procainamide (2,13). There are also case reports of pharmacodynamic interactions of fluoroquinolones with cyclosporine and possibly tacrolimus, resulting in nephrotoxicity (13). Addition of foscarnet therapy in patients taking ciprofloxacin has been associated with tonic-clonic seizures, thought to be a pharmacodynamic interaction (26).

Trimethoprim-Sulfamethoxazole

Trimethoprim and sulfamethoxazole are precipitant drugs in interactions mediated by alterations of hepatic biotransformation, competitive renal excretion, or pharmacodynamic effects (Table 2). Trimethoprim inhibits sodium channels in the distal tubules of the kidneys much like pentamidine or the potassium-sparing diuretics amiloride and triamterene. Trimethoprim has caused hyperkalemia in the elderly, in patients with the acquired immunodeficiency syndrome (AIDS), and when added to therapy with potassium-sparing diuretics or potassium supplements, including salt substitutes (27). Combined treatment with trimethoprim and thiazide diuretics has resulted in severe hyponatremia (28,29). Inhibition by trimethoprim of renal tubular excretion of amantadine, dapsone, digoxin, methotrexate, procainamide, and zidovudine has also been reported in cases of toxicity of these object drugs (2,13,14).

Sulfa drugs, including sulfisoxazole and trimethoprim-sulfamethoxazole, have been commonly associated with enhancing warfarin-induced anticoagulation. The mechanism of this interaction is not known. A modest displacement of warfarin from plasma protein binding sites occurs, but this is unlikely to be a major effect (19). The results from studies of circulating levels of either enantiomer of warfarin are conflicting (30–32), but sulfamethoxazole may inhibit CYP2C9, the major cytochrome P450 isoenzyme responsible for metabolism of the more potent S-warfarin (33). O’Reilly et al (32) suggest that the interaction of trimethoprim-sulfamethoxazole and warfarin may be pharmacodynamic. Some authorities monitor prothrombin times more frequently with combined warfarin and trimethoprim-sulfame-
Trimethoprim-sulfamethoxazole in combination with methotrexate may cause bone marrow suppression. Sulfadraugs may displace methotrexate from plasma protein binding sites resulting in transiently higher levels of unbound methotrexate. Additionally, trimethoprim competes with methotrexate for renal tubular elimination. Finally, a pharmacodynamic effect of combined inhibition of dihydrofolate reductase can result in acute megaloblastic anemia when trimethoprim is added to chronic methotrexate therapy (2,13,14,34). This combination is sufficiently hazardous as to be contraindicated.

Either trimethoprim or sulfamethoxazole may substantially diminish cyclosporine levels, resulting in transplant rejection (2,13). Trimethoprim may also have a pharmacodynamic effect of causing a rise in serum creatinine level in patients on cyclosporine. There are case reports of leukopenia resulting from a pharmacodynamic interaction of trimethoprim and azathioprine (14).

For unknown reasons, the effects of several drugs may be diminished when patients are also treated with trimethoprim-sulfamethoxazole, including oral contraceptives, pimozide, and 6-mercaptopurine (14).

**Table 2. Drug Interactions Involving Trimethoprim-Sulfamethoxazole**

<table>
<thead>
<tr>
<th>Interacting Drug (Reference)</th>
<th>Effect of Trimethoprim-Sulfamethoxazole</th>
<th>Action Prescriber Should Take</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine (14)</td>
<td>Leukopenia</td>
<td>Monitor leukocyte count</td>
</tr>
<tr>
<td>Cyclosporine (2,13)</td>
<td>Decreased cyclosporine level; azotemia</td>
<td>Monitor levels, renal function</td>
</tr>
<tr>
<td>Dapsone (2,13,14)</td>
<td>Methemoglobinemia</td>
<td>Monitor methemoglobin level</td>
</tr>
<tr>
<td>Digoxin (2,13,14)</td>
<td>Increased digoxin level</td>
<td>Monitor digoxin level</td>
</tr>
<tr>
<td>Methotrexate (2,13,14,34)</td>
<td>Leukopenia, stomatitis</td>
<td>Avoid; use folinic acid; monitor leukocyte count</td>
</tr>
<tr>
<td>Metronidazole (13)</td>
<td>Disulfiram reaction (intravenous trimethoprim-sulfamethoxazole)</td>
<td>Avoid</td>
</tr>
<tr>
<td>Phenytoin (2,13,14)</td>
<td>Phenytoin toxicity</td>
<td>Monitor phenytoin level</td>
</tr>
<tr>
<td>Potassium (27)</td>
<td>Hyperkalemia</td>
<td>Avoid; monitor serum potassium level</td>
</tr>
<tr>
<td>Potassium-sparing diuretics (27)</td>
<td>Hyperkalemia</td>
<td>Avoid; monitor serum potassium level</td>
</tr>
<tr>
<td>Procainamide (2,13,14)</td>
<td>Procainamide toxicity</td>
<td>Monitor levels; electrocardiogram</td>
</tr>
<tr>
<td>Rifampin (71,79)</td>
<td>Increased rifampin level</td>
<td>Observe</td>
</tr>
<tr>
<td>Sulfonylurea hypoglycemics (2,13,14)</td>
<td>Increased hypoglycemic effect</td>
<td>Monitor serum glucose level</td>
</tr>
<tr>
<td>Thiazide diuretics (28,29)</td>
<td>Hyponatremia</td>
<td>Monitor serum sodium level</td>
</tr>
<tr>
<td>Warfarin (32,33)</td>
<td>Enhanced anticoagulation</td>
<td>Avoid; monitor prothrombin time</td>
</tr>
<tr>
<td>Zidovudine (2,13,14)</td>
<td>Cytopenias (in hepatic failure)</td>
<td>Monitor complete blood count</td>
</tr>
</tbody>
</table>

Macrolide Antibiotics

Macrolide antibiotics differ in their abilities to bind to and inhibit cytochrome P450 isoforms, especially CYP3A4. These differences allow macrolides to be classified into three groups that correlate closely with inhibitory precipitant interactions with several drugs (35–39). Group 1 agents include erythromycin and troleandomycin; these bind strongly to and inhibit CYP3A4. They are associated with the most important object drug toxicities. Group 2 macrolides (clarithromycin) have intermediate binding affinity to CYP3A4. Group 3 agents include azithromycin and dirithromycin, which do not bind CYP3A4 and are associated with the fewest adverse interactions (35,36,40). Because of the interindividual variation in CYP3A4 activity, macrolide interactions are not predictable.

**Macrolides as object drugs.** Ethanol decreases the absorption of erythromycin ethylsuccinate, and food modestly decreases the absorption of all macrolides except clarithromycin and enteric-coated erythromycins. The metabolism of group 1 and group 2 macrolide antibiotics by CYP3A4 is inhibited by ritonavir, which may be advantageous in the management of infections caused by Mycobacterium avium complex. Cimetidine also inhibits microsomal P450 metabolism and has been associated with transient reversible deafness due to high-dose erythromycin (41).

**Macrolides as precipitant drugs.** A few pharmacokinetic interactions in which macrolides are the precipitant drug are common or dangerous. The object drugs in these interactions include astemizole, terfenadine, carbamazepine, cisapride, clozapine, cyclosporine, digoxin, ergot alkaloids, pimozide, tacrolimus, theophylline, and warfarin (Table 3). The nonseminating H1 antihistamines astemizole and terfenadine are both metabolized by CYP3A4 and will accumulate if a potent inhibitor of CYP3A4 is coadministered. These antihistamines cause a dose-dependent prolongation of the QTc interval and, rarely, tordades de pointes. Group 1 and group 2 (but not group 3)
macrolides, by inhibiting CYP3A4, have been associated with approximately 10% of the reported cases of terfenadine cardiotoxicity (42–45). Because of its potential toxicity, terfenadine has been withdrawn from the US market, and patients should be instructed to discard any that they have stored. A similar pharmacokinetic interaction occurs between macrolides and loratadine, but loratadine is not cardiotoxic.

Inhibition by group 1 and 2 macrolides of CYP3A4 metabolism of carbamazepine can result in carbamazepine toxicity within one to several days (2,13). Azithromycin and dirithromycin have not been associated with this interaction, but as a rule, macrolides should not be prescribed for patients on carbamazepine.

Cisapride can prolong the QTc interval. It is also metabolized by CYP3A4. Although no cases of cardiotoxicity from the combination of cisapride with macrolide therapy have been reported, the manufacturer’s package insert notes ventricular arrhythmias with erythromycin or clarithromycin therapy and recommends avoiding coprescription of group 1 and 2 macrolides with cisapride (13).

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Group 1 and 2 macrolides can inhibit the metabolism of cyclosporine, resulting in its accumulation and toxicity (2,14,46). This effect may be immediate (within hours) and occurs whether the macroide is given orally or intravenously. There has also been a report of cyclosporine toxicity with concurrent azithromycin therapy, and small increases in cyclosporine levels are also precipitated by dirithromycin. Erythromycin may lead to elevated tacrolimus levels and toxicity in organ transplant recipients (47,48).

Ergot alkaloids are prescribed infrequently, but a severe interaction can occur during concurrent therapy with the group 1 macrolides troleandomycin or erythromycin, leading to acute ergotism that can result in limb amputation (2).

Pimozide, used for treatment of Tourette’s disorder, can cause prolongation of the QTc interval and is metabolized by CYP3A4. Two sudden deaths have occurred during concurrent treatment with clarithromycin, so the Food and Drug Administration has determined that all macrolides are contraindicated with pimozide (49).

Combined therapy with theophylline and group 1 or 2 macrolides should be avoided or, if these drugs must be used coincidently, vigilance should be heightened for theophylline accumulation and toxicity.

Erythromycin has been reported to cause excessive hypoprothrombinemia and serious bleeding in several patients on previously stable warfarin doses. Pharmacokinetic studies show a modest effect of erythromycin in decreasing warfarin clearance, presumably by inhibition of cytochrome P450 isozymes important in warfarin metabolism (2,13).

**Azole Antifungals**

The mechanisms of interactions involving the azole antifungals, specifically ketoconazole, itraconazole, and fluconazole, include alterations of solubility and absorption of the azole, as well as modified P450 biotransformation of either the azole or the other drug in the interacting pair.

**Azole antifungals as object drugs.** Ketoconazole and itraconazole are soluble at acid pH but only 10% soluble at pH 6. Antacids, including the buffer that stabilizes didanosine, and inhibitors of gastric acid secretion including H2 antihistamines and proton pump inhibitors, decrease the bioavailability of these two azoles. Sucralfate decreases absorption of ketoconazole to a lesser degree. Ketoconazole or itraconazole should be given at least 2 hours before antacids or sucralfate. During concurrent treatment with H2 antihistamines or proton pump inhibitors, absorption can be enhanced if ketoconazole or itraconazole is taken with a cola drink or other acidic bev-
**Drug Interactions and Anti-infective Therapy/Gregg**

**Table 4. Drug Interactions Involving the Azole Antifungals Ketoconazole, Itraconazole, and Fluconazole**

<table>
<thead>
<tr>
<th>Interacting Drug (Reference)</th>
<th>Effect of Azole</th>
<th>Action Prescriber Should Take</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiolytics* (2,13,14,62–64)</td>
<td>Sedation (K, I)</td>
<td>Consider alternative drugs</td>
</tr>
<tr>
<td>Astemizole (2,13,14,57,59)</td>
<td>Increased QTc interval; torsades de pointes</td>
<td>Avoid; monitor QTc interval</td>
</tr>
<tr>
<td>Cisapride (2,13,14,60)</td>
<td>Increased QTc interval; torsades de pointes (K&gt;=1, F)</td>
<td>Avoid; monitor QTc interval</td>
</tr>
<tr>
<td>Cyclosporine (2,13,61)</td>
<td>Increased cyclosporine level; azotemia</td>
<td>Monitor cyclosporine level, renal function</td>
</tr>
<tr>
<td>HMGCoA reductase inhibitors† (13,68)</td>
<td>Rhabdomyolysis</td>
<td>Avoid</td>
</tr>
<tr>
<td>Methylprednisolone (2,14)</td>
<td>Adrenal suppression (K)</td>
<td>Avoid K; decrease dose of methylprednisolone</td>
</tr>
<tr>
<td>Phenyoctin (2,14,51)</td>
<td>Phenytoin toxicity (F)</td>
<td>Avoid F; monitor phenytoin level</td>
</tr>
<tr>
<td>Tacrolimus (2,13)</td>
<td>Increased tacrolimus level, azotemia</td>
<td>Monitor tacrolimus level, renal function</td>
</tr>
<tr>
<td>Terfenadine (2,13,14,54–58)</td>
<td>Increased QTc interval; torsades de pointes</td>
<td>Avoid; monitor QTc interval</td>
</tr>
<tr>
<td>Warfarin (2,13,14,65,66)</td>
<td>Enhanced anticoagulation (esp F)</td>
<td>Monitor prothrombin time</td>
</tr>
</tbody>
</table>

* Alprazolam, buspirone, clordiazepoxide, diazepam, midazolam (oral), triazolam.
† Especially atorvastatin, lovastatin, simvastatin.
K = ketoconazole; I = itraconazole; F = fluconazole.

Age, or if the new liquid formulation of itraconazole is used. In contrast to ketoconazole, the absorption of itraconazole is maximal if it is taken with a meal (50). Fluconazole does not depend on gastric acidity or food for its dissolution or absorption.

Rifampin and to a lesser degree rifabutin induce several P450 isoenzymes that increase the metabolism of ketoconazole and itraconazole but have minimal effect on fluconazole. Ketoconazole levels have been decreased 80%, and itraconazole has been undetectable during rifampin treatment (51,52), resulting in antifungal treatment failures (51). A similar induction of ketoconazole or itraconazole metabolism occurs with concurrent phenytoin or carbamazepine therapy (51).

In several case reports, isoniazid treatment decreased concurrent ketoconazole serum concentration by as much as 80% with failure of ketoconazole treatment (2). The mechanism of this interaction may be enhanced metabolism of the azole.

**Azole antifungals as precipitant drugs.** Precipitant interactions involving azole antifungals result from their inhibition of cytochrome P450 enzymes (Table 4). The differences within this class of drugs lie in the different isoenzyme specificity of fluconazole (principally CYP2C9) compared with ketoconazole and itraconazole, which inhibit CYP3A4. Large doses (eg, 800 mg per day) of fluconazole also can inhibit CYP3A4 (53).

The most serious interactions are with the nonsestating antihistamines terfenadine and astemizole, as discussed above in the section on macrolide antibiotics. Ketoconazole and itraconazole have been most commonly reported with this interaction (54–59). Fluconazole has a lesser effect but can result in a prolonged QTc interval in patients on concurrent terfenadine (53). Cisapride can also cause a prolonged QTc interval and accumulates in the presence of CYP3A4 inhibitors including azole antifungals. Fatalities have been reported to the manufacturer of cisapride (60).

Azole antifungals inhibit the CYP3A4 metabolism of cyclosporine and tacrolimus, which can result in toxicity. Ketoconazole is a more potent inhibitor of cyclosporine metabolism than are itraconazole or fluconazole (2,13), and has been used for cyclosporine dose sparing (13,61). Tacrolimus can be used safely with fluconazole if its dose is reduced (2,13).

The metabolism of orally administered midazolam, triazolam, and other anxiolytics that are oxidized by CYP3A4 are inhibited by ketoconazole or itraconazole therapy (62,63) more than by fluconazole (64). This effect is not seen with intravenous midazolam, the only form of this drug currently available in the United States. With either midazolam or triazolam, peak concentrations are increased fourfold, and the half-life doubled or tripled, leading to excessive and prolonged sedation. If given to a patient on ketoconazole or itraconazole neither of these drugs should be considered as short-acting benzodiazepines (2).

Fluconazole, but not ketoconazole or itraconazole, increases the plasma concentrations of phenytoin, presumably as a result of inhibition of phenytoin biotransformation by CYP2C9. There are case reports of phenytoin toxicity (2,14).

S-warfarin is hydroxylated by CYP2C9, and the less potent R-warfarin is metabolized in part by CYP3A4. There is substantial evidence that fluconazole by its inhibition of CYP2C9 increases the effect of warfarin on coagulation (65,66). No warfarin interactions have been reported as a result of vaginally or cutaneously applied azoles (14).

Other drugs, including felodipine, quinidine, HMG CoA reductase inhibitors (statins), and sulfonlyurea hypoglycemic agents, may occasionally accumulate during
significant interaction occurs with cyclosporine, tacrolimus, itraconazole, and warfarin, necessitating substantially increased doses of the object drug or alternative therapy (2,13,14,67,68). Anterior uveitis caused by rifabutin has resulted from concurrent fluconazole or itraconazole therapy in patients with AIDS; ketoconazole may have the same effect.

**Rifamycins**

Rifampin is the most potent and broadly specific inducer of cytochrome P450 isoenzymes, including CYP1A2, the CYP2C subfamily, and CYP3A4. Rifabutin, whose anti-inflammatory value is largely limited to treatment of *Mycobacterium avium* infections, is a less potent P450 inducer. Both rifampin and rifabutin may be either object or, more importantly, precipitant drugs. In all of the important precipitant interactions, the rifamycins induce P450 metabolism of the object drug, reducing its bioavailability, plasma concentrations, and often its half-life, which sometimes results in failure of therapy with the object drug (12,51,69–71).

**Rifamycins as object drugs.** Aluminum hydroxide antacids, ketoconazole, or pyrazinamide can reduce the oral bioavailability of rifampin. Concurrent administration of rifabutin with clarithromycin (72), fluconazole, or itraconazole has resulted in high rifabutin serum levels that can result in chronic uveitis or other therapy-limiting effects such as polyarthralgia (73–77). The HIV-1 protease inhibitors indinavir, nelfinavir, and ritonavir, and the non-nucleoside reverse transcriptase inhibitor delavirdine, are potent inhibitors of CYP3A4 and other P450 isoforms (12,78). As a result of concern for the possibility of interaction with these drugs, rifampin is contraindicated with indinavir, ritonavir, and delavirdine and not recommended with saquinavir or nelfinavir. If rifabutin is to be used with protease inhibitors, the dose of rifabutin should be reduced by 50% to 75% or an alternative drug considered (78). Rifabutin is contraindicated with delavirdine because of rifabutin toxicity and induction of delavirdine metabolism. Trimethoprim-sulfamethoxazole can also raise rifampin levels (71,79).

**Rifamycins as precipitant drugs.** There are many object drugs whose metabolism is induced by concurrent treatment with rifampin or rifabutin (Table 5). Major induction interactions have occurred between rifamycins and corticosteroids, resulting in decreased steroid effects in patients with Addison’s disease, asthma, nephrotic syndrome, organ transplants, and giant cell arteritis (2,13,14,69,70). These effects can occur within days and can be clinically important. Similar interactions occur with cyclosporine, tacrolimus, itraconazole, and warfarin, necessitating substantially increased doses of the object drugs or alternative therapy (2,13,14,69,70,80). When therapy with a rifamycin is discontinued there is usually a washout period of 1 to 3 weeks during which cytochrome P450 metabolism returns to baseline. Object drug levels may increase during that time resulting in toxicity if the dose is not adjusted. This effect has been important in therapy with cyclosporine, tacrolimus, sulfonamide hypoglycemics, theophylline, quinidine and warfarin (2).

Rifampin interacts with isoniazid by inducing a secondary metabolic pathway that converts isoniazid to hydrazine, which is hepatotoxic. This interaction can result in severe hepatitis in persons (especially children) who are slow acetylators of isoniazid (2).

A relatively uncommon interaction of rifampin with digoxin or digitoxin resulting in decreased digitalis levels has been described in patients with renal failure who depend on non-renal (hepatic) elimination of digitalis glycosides. Rifampin induces this metabolic pathway, and the digoxin dose may need to be increased by 35% to 100% to maintain therapeutic levels. The digoxin dose should be decreased by 50% when rifampin is discontinued (70).

**Metronidazole**

Because of its well-known ability to precipitate a disulfiram-like reaction when taken concurrently with ethanol, metronidazole should be used cautiously in patients concurrently using oral tinctures or intravenous medications containing ethanol (eg, diazepam, nitroglycerin, phenobarbital, phenytoin, and trimethoprim-sulfamethoxazole) (13). Two additional potentially serious metronidazole interactions are its enhancement of the toxicity of fluorouracil and of the effect of warfarin (2,13).
**Antiretroviral Agents**

Patients with human immunodeficiency virus (HIV) infection are typically prescribed several drugs, including combination antiretroviral regimens as well as antimicrobial agents for prophylaxis or treatment of opportunistic infections, and other medications that may interact with their antiretroviral drugs. Moreover, these patients may receive prescriptions from more than one physician, and many take nonprescription drugs. The net effect is a multitude of possible pharmacokinetic or pharmacodynamic drug interactions, many of which have already been discussed. This section will address the antiretroviral drugs as object and precipitant drugs, focusing on those that have a substantial clinical impact (12,78,81–85).

**Nucleoside analogues.** Of the currently available nucleoside HIV-1 reverse transcriptase inhibitors, zidovudine is most likely to be involved in an adverse drug interaction. It is the object drug in several pharmacokinetic interactions and one serious pharmacodynamic interaction. Pharmacokinetic drug interactions that can cause elevated zidovudine levels result from inhibition of its glucuronidation in the liver (by atovaquone, fluconazole, interferon-β, methadone, or valproate), renal excretion (trimethoprim), or both (probenecid). Drugs such as cimetidine, probenecid, or imipramine that compete with renal elimination of zidovudine or of its toxic metabolite could contribute to zidovudine toxicity, especially in patients with hepatic dysfunction (85). These interactions are unpredictable because of day-to-day variations in zidovudine elimination. Hepatic glucuronidation is induced by the rifamycins, and fatty meals inhibit absorption of zidovudine, either of which can result in its decreased bioavailability (2).

High-dose zidovudine interacts pharmacodynamically with ganciclovir to cause neutropenia in many patients. Although most physicians now use lower doses of zidovudine (eg, 600 mg per day) in routine care, the addition of another drug that raises zidovudine levels could potentiate this interaction. Thus, zidovudine should not be prescribed for patients on ganciclovir.

Combined therapy of HIV infection using zidovudine plus stavudine has resulted in unexpectedly poor clinical, immunologic, and virologic responses, perhaps because zidovudine may inhibit the intracellular phosphorylation of stavudine (86).

Didanosine may interact pharmacodynamically with several drugs to cause peripheral neuropathy (cisplatin, isoniazid, metronidazole, nitrofurantoin, ribavirin, stavudine, vincristine, zalcitabine) or pancreatitis (ethanol, lamivudine, pentamidine). Similarly, zalcitabine, stavudine, and possibly lamivudine can be neurotoxic (78) and may rarely cause pancreatitis. Pharmacokinetic interactions of didanosine include the effect of its buffer, which not only chelates several fluoroquinolones but also, by neutralizing gastric acid, decreases the absorption of drugs that require a low pH for solubility (dapsone, indinavir, itraconazole, ketoconazole, pyrimethamine, rifampin, trimethoprim).

**Non-nucleoside reverse transcriptase inhibitors.** Nevirapine and delavirdine are two non-nucleoside reverse transcriptase inhibitors currently available in the United States. Both are metabolized by hepatic P450 enzymes, principally CYP3A4. Few clinically important pharmacokinetic interactions have been described, and recommendations on their combined use with other drugs come from in vitro testing and unpublished data. Nevirapine induces CYP3A4 and may reduce the effects of coadministered oral contraceptives and HIV-1 protease inhibitors. However, increased dosage of the protease inhibitors is not currently advised when used in combination with nevirapine (78).

By contrast delavirdine inhibits CYP3A4 (87), which can increase the concentration of other substrates of this P450 isoform, including HIV-1 protease inhibitors (78,88). The metabolism of delavirdine by the same enzyme is induced by carbamazepine, phenobarbital, phenytoin, and rifamycins. Concurrent therapy with alprazolam, astemizole, cisapride, dihydropyridine calcium channel blockers, ergot alkaloids, midazolam, rifabutin, rifampin, or triazolam is inadvisable for patients being treated with delavirdine.

**HIV-1 protease inhibitors.** The HIV-1 protease inhibitors indinavir, nelfinavir, saquinavir, and ritonavir are all metabolized by CYP3A4, but ritonavir is also a substrate of CYP2C9 and CYP2D6 (12,78,81,83). This broader isoenzyme specificity of ritonavir and its avid P450 binding characteristics explain why there are more drug interactions for ritonavir. In addition, ritonavir induces glucuronyl transferase, which diminishes the effects of oral contraceptives and theophylline. Saquinavir was the least bioavailable protease inhibitor until a recent reformulation was released. It also has the least potent CYP3A4 inhibitory effects. P450 interaction among protease inhibitors has led to the intentional combined use of saquinavir and low dose ritonavir, which results in greatly increased bioavailability (50- to 100-fold) of saquinavir with acceptable adverse effects. Other analogous combination protease inhibitor therapies are under investigation (78).

Saquinavir levels are increased by concurrent ritonavir, ketoconazole, group 1 and 2 macrolides, delavirdine, or grapefruit juice, and decreased by rifampin and rifabutin. Because it, too, is a CYP3A4 inhibitor, saquinavir is not recommended for combined use with astemizole, cisapride, or ergot alkaloids. However, there are as yet no
reports of adverse clinical outcomes resulting from these combinations.

Indinavir is a substrate for, and potent inhibitor of, CYP3A4. Like the other protease inhibitors, its levels are increased by ketoconazole and decreased by rifampin or rifabutin. Because of its inhibition of CYP3A4, indinavir is not recommended for concurrent use with amiodarone, cisapride, ergot alkaloids, midazolam, rifampin, or triazolam. Indinavir also inhibits the metabolism or excretion of zidovudine, stavudine, clarithromycin, rifabutin, and trimethoprim. For instance, rifabutin should be given at one half the usual dose if prescribed with indinavir (78). Nelfinavir is roughly equivalent to indinavir as a CYP3A4 inhibitor (89), and current recommendations on drugs to avoid for patients taking nelfinavir are the same as for indinavir.

By inducing glucuron transferase, ritonavir accelerates the metabolism and elimination of ethinyl estradiol, theophylline, sulfamethoxazole, and zidovudine. However, the most important predicted ritonavir interactions involve its inhibition of CYP2C9, CYP2D6, or CYP3A4. Many potential object drugs with a low therapeutic index are listed by the manufacturer as contraindicated because of the risk of toxicity, although there are only rare reports of adverse clinical outcomes resulting from these combinations.

Table 6. Drugs to Avoid with Ritonavir (6,12,13,60,78,90)

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesics</td>
<td>Meperidine, methadone, piroxicam, propanoxyphene</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>Amiodarone, encaïnide, flecanide, propafenone, quinidine</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Rifabutin,* rifampin</td>
</tr>
<tr>
<td>Antivirals</td>
<td>Nevirapine</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Astemizole, terfenadine</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>Bepridil</td>
</tr>
<tr>
<td>Contraceptives, oral</td>
<td>Ethinyl estradiol</td>
</tr>
<tr>
<td>Ergot alkaloids</td>
<td>All</td>
</tr>
<tr>
<td>Gastrointestinal drugs</td>
<td>Cisapride</td>
</tr>
<tr>
<td>Hypnotics, anxiolytics</td>
<td>Alprazolam, clorazepate, diazepam, estazolam, flurazepam, midazolam, triazolam, zolpidem</td>
</tr>
<tr>
<td>Other</td>
<td>Bupropion, carbamazepine, clozapine, desipramine, pimozone</td>
</tr>
</tbody>
</table>

* Rifabutin may be used at a dose of 150 mg every other day.

**RECOGNITION AND PREVENTION OF DRUG INTERACTIONS**

Although there are several text-based and computerized database references that may be useful to physicians and pharmacists, no single resource is ideal (91). The text *Drug Interaction Facts* (2) is useful because it is portable, relatively inexpensive, and provides a comprehensive review of drug pairs that have been marketed for at least a few years or that have been studied extensively. *Hansten and Horn’s Drug Interactions Analysis and Management* (13) is continually updated, thorough, and has a more practical severity rating than *Drug Interaction Facts*, but it is bulky. Several computer database programs on drug interactions are available (14,92,93), but these vary widely in their quality, cost, and ease of use. *The Medical Letter Drug Interaction Program* (14) was used for this review because it is relatively inexpensive, updated quarterly, and user-friendly. It includes many recently released drugs, but its discussions are brief, and it does not classify interactions by severity or incidence.

Pharmacists using computer technology have a growing role in preventing serious adverse drug interactions (94). Because the knowledge base for drug interactions is so large, such preventive intervention appears to be a necessary safeguard in medical practice.

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